At the outset, please label any future communications with the new docket number shown in the top margin of this paper so that the papers may be quickly matched with the appropriate file.

The specification has been amended to include reference to the priority application, and to include an abstract on a separate sheet as required in the Office Action. In addition, claim 1 has been amended in order to more clearly define the present invention. More specifically claim 1 has been amended in order to stress the anti-tumor nature of the claimed compositions, and in order to emphasize a general aspect of the invention, that the polypeptides in the claimed compositions are not fused. Support for this amendment may be found in the examples of the present application, where all the experiments described have been conducted with constructs producing non-fused early and late polypeptides whose expression is controlled by independent regulatory elements. No new matter has been added.

In addition, new claims 32 and 33 have been added, which are directed to two compositions particularly exemplified in the application. For instance, claim 32 finds support in Example 2, beginning on page 21, and claim 33 finds support in Example 1, beginning on page 16. No new matter has been added.

Turning now to the Office Action, Applicants acknowledge with appreciation the Examiner's decision to prosecute claims 23 and 24 along with the elected group. With the new claims added above, claims 1, 3-9, 21, 23, 24, 32 and 33 are now pending.

Claims 5, 8, and 9 were rejected under 35 U.S.C. §112, second paragraph for alleged lack of clarity concerning the phrase "according to one of claim . . .". Applicants respectfully submit that the indicated phrase was deleted from these claims by way of the Preliminary Amendment filed March 30, 1998. Accordingly, withdrawal of the rejection and correction of the claims in the file history is respectfully requested.

Next, claims 1-9, 21, 23 and 24 were rejected under 35 U.S.C. §102(e) as being anticipated by two different Lowy et al. U.S. patents and under 102(a) by one published Lowy PCT. Applicants respectfully traverse each of the rejections based on Lowy.

Firstly, it is noted that all the Lowy patents cited belong to the same patent family and differ only by the claims. Thus, it seems appropriate to address each of the references together because they have the same disclosure. Each Lowy patent describes chimeric papilloma pseudo particles (VLP) based on self assembled L1 and L2 polypeptides exhibiting at their surface an early papilloma epitope (E6 or E7). The targeting of the early epitope to the surface of the VLP is obtained by fusing the sequence encoding the early epitope to the gene encoding the VLP component. Example 1 of the Lowy patents illustrates various L2/E7 fusions involving two different strains of papillomavirus (bovine BPV or human HPV16), two different E7 polypeptides (full length or N-terminal residues 1-30), and two different fusion sites (C-terminus or between residues 274 and 275 of L2). The L2/E7 fusion is then cloned into a baculovirus comprising the wild-type L1 gene, and chimeric VLPs are produced in vitro after infection of Sf9 insect cells. While Lowy discusses the possibility of including additional partners such as costimulatory polypeptide

B7, the teaching is limited to presentation at the surface of a VLP via fusion with one of the VLP components. For instance, the data of Lowy's Example 14 identifies the BPV L2 region contained within residues 44-173 as being suitable to fuse to such a polypeptide.

In contrast to Lowy, the papillomavirus compositions of the present invention do not contain fused early and late region polypeptides. Such is evidenced by the exemplary vectors of the present invention, none of which encode fused polypeptides. The claims have been amended to emphasize this feature of the claimed invention, thereby distinguishing the present claims from Lowy for the purposes of 35 U.S.C. §102. Because it is well settled that "[a]nticipation under § 102 requires the presence in a single prior art disclosure of all elements of a claimed invention arranged as in that claim," Carella v. Starlight Archery, 231 USPQ 644, 646 (Fed. Cir. 1986), Lewmar Marine Inc. v. Barient, Inc., 3 USPQ2d 1766, 1767 (Fed. Cir. 1987), the Lowy patents can not be applied as §102 art against the claims as amended. Reconsideration and withdrawal of the rejection in view of the amendments proposed above is respectfully requested.

Next, claim 1 was rejected under 35 U.S.C. §102(b) over Zhou et al. (hereinafter Zhou). It is the Examiner's opinion that the HPV-16 construct of Zhou meets the limitation of the claim, in that it allegedly teaches a "construct of early and late protein" of HPV-16. Applicants respectfully traverse the rejection.

Applicants respectfully submit that Zhou does not teach a composition containing early and late viral proteins as recited in the instant claims. Although the Examiner is correct to note that Zhou teaches a "construct" encoding early and late proteins, it is

apparent from a reading of the entire reference that the construct does not result in viral particles containing all three proteins, nor does Zhou ever suggest employing a combination of late proteins and early proteins in a vaccine composition.

For instance, as discussed on page 254, in the paragraph bridging columns 1 and 2:

> These data suggest that the E4 protein, held to play a role in papillomavirus assembly, does not appear to be an essential element for capsomere production and assembly *in vivo*. To test whether E4 could enhance production of virus-like particles in our system, CV-1 cells were infected with the HPV16 L1, L2, and E1/E4 triple recombinant virus . . . but no quantitative or qualitative differences in virus-like particles were observed to support a role for the E1/E4 protein in capsomere assembly. This conclusion is supported by the observation that the E1/E4 protein, as demonstrated by immunofluorescence, remains in the cytoplasm of E1/E4 recombinant vaccinia virus infected cells . . . while the structural proteins L1 and L2, which contain a nuclear targeting signal . . . move from the cytoplasm to the nucleus, where the capsomeres are produced and virions assembled.

Thus, although Zhou employs a viral *construct* encoding L1, L2 and E4 for the purpose of evaluating the role of E4 in capsomere assembly, the E4 protein is not incorporated into the capsomeres themselves. Thus, Zhou does not teach a "composition" comprising an early protein to be used for vaccine purposes, because Zhou only discloses "HPV-like particles" for use as a vaccine which do not incorporate early protein. Thus, Zhou does not constitute §102 art as applied to claim 1, because claim 1 is directed to a polypeptide composition comprising both early and late viral proteins. Withdrawal of the §102 rejection based on Zhou is respectfully requested.

Claims 1-9, 21, 23 and 24 were also rejected for being unpatentable over Zhou under 35 U.S.C. 103(a), in view of Heck et al. and Robinson et al. Essentially, it is the

Examiner's opinion that the cited references provide "teaching, and motivation for one of ordinary [skill] in the relevant art to fuse a early and late proteins . . . in addition to a co-stimulatory molecule to generate a vaccine against papillomavirus" (Office Action, page 8). Applicants respectfully traverse the rejection.

First of all, to clarify the record, neither the present application nor Zhou deals with "fusions" of early to late proteins. This was the subject of the Lowy patents, none of which are cited in the present rejection. Notwithstanding this description of Zhou's compositions, the Examiner relies upon Zhou for teaching the use of a vaccine polypeptide composition containing early and late papillomavirus proteins, in effect suggesting that it would be obvious to substitute the E4 protein in Zhou's VLP particles with the E7 protein as disclosed in Heck, as well as add a costimulatory molecule as allegedly suggested by Robinson.

Applicants respectfully submit that one of ordinary skill would certainly not be motivated to *substitute* the E4 protein used in Zhou to achieve the compositions claimed in the present invention, because the E4 protein mentioned in Zhou is not incorporated into Zhou's VLPs. In fact, Zhou induces expression of E4 in his system solely to evaluate the role of E4 in papillomavirus assembly, and finds, in direct contradiction to what was believed previously, that E4 was not necessary for VLP assembly. Moreover, Zhou teaches that the E4 protein actually remains in the cytoplasm while the late proteins are incorporated into capsomeres in the nucleus (see page 254, paragraph bridging columns 1 and 2, cited above), thereby negating the argument that one would even expect to achieve

compositions comprising both early and late proteins using the teachings of Zhou. Indeed, Zhou teaches that expression of late proteins L1 and L2 is "sufficient" for VLP assembly (see page 255, col. 1, first paragraph of the discussion).

The present invention, in contrast, claims polypeptide compositions (not a viral vector as used in Zhou) comprising an early protein and a late protein from a human papillomavirus. The Examiner apparently reads Zhou as teaching a vector encoding a fusion of early (E4) and late proteins, whereby the early protein is incorporated into the VLP, and argues that it would allegedly be obvious in view of Heck to substitute the E7 gene to express E7 protein as employed in the present invention. Yet the Examiner has misinterpreted the invention, because nowhere in the application do the applicants disclose the use of fusion proteins. Claim 1 has been amended above to emphasize this aspect of the invention.

Thus, the compositions disclosed in Zhou are inherently different than those claimed in the present invention, in that the compositions of the present invention do not employ virus-like particles (VLPs). Moreover, as explicitly taught in Zhou, the E4 protein is not incorporated into VLPs, and one could not simply "substitute" E4 as used in Zhou with E7 as suggested in the present application and achieve the invention because E4 is not present in the polypeptide compositions disclosed in Zhou. Neither Heck nor Robinson remedy this basic deficiency, because neither Heck nor Robinson teach combining an early protein with a late protein to produce a polypeptide composition.

In view of the above arguments and the deficiencies of the Zhou reference as applied to the instant claims, reconsideration and withdrawal of the rejection is respectfully requested.

Should the Examiner have any questions concerning the subject application or this Reply, a telephone call to the undersigned would be appreciated.

Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

By: _____
Bonnie D. Weiss
Registration No. 43,255

P.O. Box 1404
Alexandria, Virginia 22313-1404
(703) 836-6620

Date: February 3, 2000